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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/817,360	03/20/2001	Michael S. German	UCSF-129CIP	2345

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EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 03/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/817,360	GERMAN, MICHAEL S.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/4/03*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-14,16,18-23,25,27-30 and 37-40* is/are pending in the application.

4a) Of the above claim(s) *14,16,22 and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12,13,18,19,21,28,29 and 37-40* is/are rejected.

7)☒ Claim(s) *20,25,27, and 30* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice To Comply*.

DETAILED ACTION

Final Rejection

Claims 12-14, 16, 18, 19, 20, 21, 22, 23, 25, 27-30, and 37-40 are pending.

Applicants' traversal, the amendment to claims 12, 13, 19, 21, and 25, the addition of claims 37-40, and the cancellation of claims 15 and 31-36 in paper filed on 12/4/03 is acknowledged and considered.

This application contains sequence disclosures that are encompassed by the definition for nucleotide sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements for Patent Applications Containing Nucleotide Sequence Disclosures.

SEQ ID NO: 20 is listed in the specification (Figure 19A) but is not listed in the CRF.

Election/Restrictions

This application contains claims 14, 16, 22, and 23 drawn to a nonelected species without traverse in Paper No. 8.

Drawings

The drawings were received on 12/4/03. These drawings are acceptable.

Claim Objections

Claims 19, 25, 27, 28, and 29 are objected to because of the following informalities: the phrase "said introducing providing" is grammatically incorrect. Suggest amending the phrase to recite, for example: -- wherein said introduction results in expression of the transcription factor in the mammalian cell and in production of insulin in the mammalian cell --.

Claims 20-23, 38, and 40 are objected to because they depend on claim 19.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12, 13, 18, 19, 21, 28, and 29 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using a nucleic acid encoding the neuroendocrine bHLH transcription factor neurogenin3 operably linked to a promoter to produce an insulin-producing cell from a cultured pancreatic cell or cultured liver cell *in vitro*, does not reasonably provide enablement for the full scope of the claimed invention (using a nucleic acid encoding the bHLH transcription factor neurogenin3 to differentiate embryonic stem cells or other gastrointestinal organ cells into insulin-producing cells). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claimed invention is directed to producing insulin-producing cells *in vitro* and using the cells in a method for producing insulin in a mammalian subject. The field of the invention lies in differentiating cells into insulin producing cells using a nucleic acid molecule comprising a bHLH transcription factor.

The state of art at the time the application was filed and currently teaches that, "a number of transcription factors have been shown to control pancreas morphogenesis or the differentiation of the endocrine cells...Although no transcription factor has been identified thus far that selectively controls β-cell formation" (IDS, Schwitzgebel et al. Development, 127:5533-5540, 2000). Furthermore, research indicates that multiple factors are required for the various steps of pancreatic cytodifferentiation. The identification of the transcription factors required for differentiation will help in understanding the timing and ultimately the signals that induce differentiation (IDS, Sander et al., J. Mol. Med. 75:327-340, 1997).

Thus, in view of the state of the art at the time the application was filed and currently, using a genus of nucleic acid molecules encoding a bHLH transcription factor for producing any type of insulin-producing cell *in vitro* is considered unpredictable.

The specification provides examples that will be briefly discussed herein:

Examples 1-3 are directed to isolation and production of the murine and human Ngn protein. Examples 4 and 15 are directed to constructing a vector encoding the murine Ngn3. Example 5 displays the induction of insulin in normal adult rats by treatment with the vector from Example 4. Examples 6, 16, and 17 display or contemplate the normalization of blood

glucose levels in diabetic induced adult rats using the vector from 4 or 15. Example 7 is directed to overexpression of Ngn3 in transgenic mice. Example 8 is directed to the islet cell production in NeuroD1 transgenic mice. Examples 9 and 10 contemplate the construction of adenovirus vector comprising the human or mouse neuorD1 coding sequence or ACL1/ASH1 coding sequence and examples 11 and 12 contemplate using either vector to induce the formation of insulin producing beta cells in normal adult rats. Examples 13 and 14 contemplate production of insulin in diabetic induced adult rats by the introduction of DNA encoding either neuorD1 coding sequence or ACL1/ASH1 coding sequence. Example 18 contemplates induction of the formation of islet cell *in vitro* (The Declaration by Dr. German under 1.132 teaches that gene transfer of ngn3 into mPAC cells and liver cells produced insulin *in vitro*). Example 19 contemplates delivery of Ngn3 to human subjects. Example 20 is characterization of the Ngn3 promoter.

Furthermore, with respect to claims 12, 13, 18, 19, 21, 28, and 29, the claims embrace using either a precursor cell or a mammalian cell, wherein said precursor cell or mammalian cell is an embryonic stem cell or a gastrointestinal organ cell. The as-filed specification teaches one skilled in the art how to make and/or use a nucleic acid encoding the neuroendocrine bHLH transcription factor neurogenin3 operably linked to a promoter to produce insulin-producing cell from a cultured pancreatic cell or a cultured liver cell *in vitro*. However, in view of the In Re Wands Factors, the full scope of the claimed methods is not considered enabled. The breadth of the term "gastrointestinal organ cell" embraces an enormous number of cells (pancreatic duct cells, pancreatic acinar cells, gut cells including crypt cells, liver cells, salivary gland cells, etc.). See Example 18, pages 46-47. The as-filed specification does not provide sufficient guidance

and/or factual evidence for one skilled in the art to reasonably extrapolate from using cultured pancreatic cells and cultured liver cells to using any other type of gastrointestinal organ cell. In addition, the as-filed specification contemplates using embryonic stem cells, but does not provide a working example using the claimed stem cells. The specification does not provide sufficient guidance and/or factual evidence for one skilled in the art to use an embryonic stem cell in the claimed method. The as-filed specification does not teach what materials (e.g., culture conditions and methods (e.g., methods to obtain, select and stimulate maturation of insulin-producing cells from embryonic stem cells) are required for differentiating embryonic cells into insulin-producing cells *in vitro*. At the time the application was filed (4/6/99), the art of record did not teach what methods and/or materials were required for differentiating embryonic stem cells into insulin-producing cells using a nucleic acid encoding an Ngn3 protein. The specification contemplates using mPAC cells (mouse ductal cells) to produce insulin-producing cells. The as-filed specification does not provide sufficient guidance and/or factual evidence for one skilled in the art to reasonably extrapolate from using mPAC cells for producing insulin-producing cells to using an embryonic stem cell or other gastrointestinal organ cells to produce insulin-producing cells.

In addition, the art of record teaches that HNF-alpha and Ngn3 are critical for activating PAX4, which controls the formation of insulin-producing beta cells (Smith et al, JBC, 2003, pages 1-25). Smith also teaches that transgenic overexpression of Neurogenin3 using pdx1 promoter drives the differentiation of a large population of endocrine cells that are largely alpha cells. The preponderance of alpha cell suggests that additional factors are important for diverting endocrine precursor cells from the alpha cell fate to the alternate endocrine lineages (page 3).

The specification does not teach which cells have PAX4 and HNF-alpha other than mammalian pancreatic cells. Smith teaches that NIH3T3 cells do not have endogenous HNF4alpha (page 14). The court in Enzo 188 F.3d at 1374, 52 USPQ2d at 1138 states:

> It is well settled that patent applications are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed.
> In re Vaeck, 947 F.2d 48, 496 & n.23. 30 USPQ2d 1438, 1445 &n23 (Fed. Cir. 1991)(citation omitted). Here, however, the teachings set forth in the specification provide no more than a "plan" or "invitation" for those of skill in the art to experiment...; they do not provide sufficient guidance or specificity as to how to execute that plan. See Fiers v. Revel. 984 F.2d.1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993); In re Wright, 999 F.2d...[1557], 1562, 27 USPQ2d...[1510], 1514. [Footnote omitted].

On this record, it is apparent that the specification provides no more than a plan or invitation to in view of the reasons set forth above to experiment with an embryonic stem cell or other gastrointestinal organ cells other than mammalian pancreatic or mammalian liver cells, for those skilled in the art to experiment with any embryonic stem cell or other types of gastrointestinal organ cells, so as to provide insulin-producing cells as intended by the as-filed specification at the time the invention was made. Thus, in view of the In re Wands Factors the full scope of the claims is not considered enabled.

In conclusion, the as-filed specification and claims coupled with the art of record at the time the invention was made only provide sufficient guidance and/or evidence to reasonably enable an *in vitro* method of producing insulin-producing cells using cultured pancreas or liver cells. Given that differentiating an embryonic stem cell or any other type of gastrointestinal organ cell into specific insulin-producing cells was unpredictable at the time the invention was made, one skilled in the art would have to engage in a large quantity of experimentation in order

to practice the claimed invention based on the applicant's disclosure and the unpredictability of differentiating cells into a specific type of cell.

Applicant's arguments filed 12/4/03 have been fully considered and are found partially persuasive.

Applicant argues that in view of Applicant's actual reduction to practice of the claimed methods using liver and pancreas cells, a skilled person would recognize that the claimed methods could be used with a wide variety of cells, including embryonic stem cells and cultured gastrointestinal organ cells, e.g., cultured liver and pancreas cells.

The argument is not found persuasive for reasons of record. In view of the breadth of the term "cultured gastrointestinal organ cell" provided by the specification (Example 18), the art of record teaches that HNF-alpha and Ngn3 are critical for activating PAX4, which controls the formation of insulin-producing beta cells (Smith et al, JBC, 2003, pages 1-25). The specification does not teach which gastrointestinal cells have PAX4 and HNF-alpha other than mammalian pancreatic cells. See Enzo 188 F.3d at 1374, 52 USPQ2d at 1138.

The lack of enablement for making and using embryonic stem cell to produce insulin-producing cells is further supported by Street et al., Current Topics in Developmental Biology, Vol. 58: 111-136, 2003. Street teaches that, "One of the major limitations in ES cell research, however, is the inability to produce well controlled, directed differentiation into specific tissue types. This heterogenous differentiation poses difficulties when attempting to create a large number of pancreatic islet cells (page 116)." Soria teaches, "there is still little knowledge on how to induce ESC into a particular endoderm path and the architectural complexity of epithelial

tissue points to the importance of cell-to-cell interactions (Diabetologia, 44:407-415, 2001). Furthermore, Soria teaches, "although Ngn3 is required for differentiation of all pancreatic lineages, when expressed alone, in combination with Pdx1, or even under the control of the Pdx2 promoter it does not induce insulin-producing cells either in the mouse or in the chicken (Differentiation, 2001, 68: 205-219). The specification does not provide sufficient guidance and/or factual evidence for one skilled in the art to use embryonic stem cells in the claimed method. In view of the In Re Wands Factors, the full scope of the claimed methods is not enabled.

In addition, with respect to applicant's assertion "in view of Applicant's actual reduction to practice of the claimed methods using liver and pancreas cells, a skilled person would recognize that the claimed methods could be used with a wide variety of cells, including embryonic stem cells and cultured gastrointestinal organ cells, e.g., cultured liver and pancreas cells," the assertion is not found persuasive because the assertion is not supported by any evidence of record. See MPEP § 716.01(c).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 37-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 37-40 recite the limitation "gastroinstestinal organ" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Response to Arguments

Applicant's arguments, filed on 12/4/03, with respect to claims objection have been fully considered and are persuasive. The objection of claims 12, 19, 31, 32, 33, 34, 35, and 36 has been withdrawn because of the amendment to claims 12 and 19 and the cancellation of claims 31-36.

Applicant's arguments, filed on 12/4/03, with respect to 112 first paragraph rejection have been fully considered and are persuasive. The rejection of claims 12, 13, 18-21, 25, 27-30 30 has been withdrawn because of the amendment to claims 12 and 19.

Applicant's arguments, filed on 12/4/03, with respect to 112 second paragraph rejection have been fully considered and are persuasive. The rejection of claims 12, 13, 21, 25, 30, 31, and 34 has been withdrawn because of the amendment to claims 12, 13, 21, and 25 and the cancellation of claims 31 and 34. However, upon further consideration, a new ground(s) of rejection is made in view of the amendment to claims 12 and 19 and the addition of claims 37-40.

Conclusion

Claim 30 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, SPE - Art Unit 1635, can be reached at (571) 272-0760.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman
Patent Examiner, Group 1635

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER